

APPLICANT(S): ROSENBERG, Robert D. et al.

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## **REMARKS**

### **Status of Claims**

Claims 1-65 are pending in the application. Claims 18, 20 and 22-31 have been objected to. Claims 3-5, 32-38, 40, 41, 49-62, 64 and 65 have been withdrawn from consideration. Claims 1, 2, 6-18, 20, 22-31, 39, 42-48 and 63 have been rejected. Claims 1-2 and claims 11 and 12 have been amended. Support for the amendments can be found, for example, at column 1 paragraph [0010], column 5 paragraph [0061] to column 7 paragraph [0078], column 8 paragraph [0087], column paragraph 9 [0093] and in the Examples. Claims 6-17, 43-44, 46-48 have been amended to remove multiple dependencies and to be directed to the elected subject matter. Claims 7, 9 and 44 were further amended. Support for the amendments can be found, for example, at column 2 paragraph [0014] and paragraph [0018]. Claim 39 has been amended to recite only Polysaccharide 15. Claim 42 has been amended to correct a typographical error. Support for amended claim 42 maybe found throughout the specification, for example, at page 24, lines 21-22, and in Figure 20 and Example 20.

### **Information Disclosure Statement (IDS)**

The Examiner has not considered Reference J submitted with the December 26, 2008 IDS because the citation did not include the Title of the Article. Applicants submit herewith a Supplemental IDS and a copy of Reference J. Applicants respectfully request that this Reference be reviewed by the Examiner and an initialed copy of the accompanying PTO SB08 Form be returned to Applicants.

## **CLAIM OBJECTIONS**

Claims 18, 20 and 22-31 have been objected to under 37 C.F.R. 1.75(c) as being improper multiply dependent claims. As amended herein, claims 18, 20 and 22-31, depend from claims 11 and 12, which are not multiple dependent claims. Accordingly, Applicants respectfully request that the objection be withdrawn.

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## **CLAIM REJECTIONS**

### **Double Patenting Rejections**

Claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 stand provisionally rejected for obviousness-type double patenting over claims 13, 18, 19, 24, 29 and 30 of copending Application No. 11/204,391. Applicants respectfully disagree.

Applicants request that the provisional obviousness-type double patenting rejection be held in abeyance until allowable subject matter has been identified, at which time Applicants will consider filing a Terminal Disclaimer.

Claims 1, 2, 6, 8, 10-18, 20 and 22-31 stand provisionally rejected for obviousness-type double patenting over claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending Application No. 10/986,058. Applicants respectfully disagree.

Applicants request that the provisional obviousness-type double patenting rejection be held in abeyance until allowable subject matter has been identified, at which time Applicants will consider filing a Terminal Disclaimer.

### **Rejections Under 35 U.S.C. § 112**

Claims 1-31 and 39 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner asserts that the terms “incompletely sulfated polysaccharide” and “incompletely sulfated heparin sulfate” in claims 1 and 2 are unclear, rendering claims 1-31 indefinite. Applicants respectfully disagree.

One of ordinary skill would readily understand that an “incompletely sulfated polysaccharide” is simply a polysaccharide that has an O- or N-site that is not yet sulfated, and is thus available for a sulfation to take place. Accordingly, Applicants believe that claims 1-31 are definite, and respectfully request that the rejection be withdrawn.

The Examiner asserts that it is not clear what is being synthesized in claim 39, or the steps involved in the synthesis. The Examiner also asserts that the structures of the polysaccharides depicted in Figures 3-5, 9 and 20 and recited in claim 39 are also unclear.

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Claim 39 has been amended to recite a method of synthesizing Polysaccharide 15 that involves the process steps outlined in Figure 20. The structure of Polysaccharide 15 has been added to the claim.

Applicants assert that the use of bonds not attached to any atoms to denote the polysaccharides disclosed is for the recognition that the polysaccharide unit at this point in the synthesis is part of a larger polysaccharide chain. Such notation is clear to a person skilled in the art. After the use of e.g. a Heparitinase I (The synthesis of 11 from 10 in Figure 20), the polysaccharide unit becomes an isolated unit, lacking the linking bonds at its ends.

Accordingly, Applicants believe that claim 39, as amended herein, is definite. Therefore, Applicants respectfully request that the rejection be withdrawn.

The Examiner asserts that there is insufficient antecedent basis for the term "chemical reagents" in claims 7 and 9, as this term is not present in claim 1 or claim 2.

Claims 7 and 9 have been amended to add reference to "wherein said method further comprises treating the ... with up to four chemical reagents". Support for the amendments can be found, for example, at column 2 paragraphs [0014] and [0018] where a combination of enzymatic and chemical processes is disclosed. Applicants assert that since claims 1 and 2 recite the transitional phrase "comprising," the method does not exclude the possibility to further treat the polysaccharide with a chemical. Accordingly, Applicants assert that claims 7 and 9 as amended are in proper format, and respectfully request withdrawal of the rejection.

The Examiner asserts that there is insufficient antecedent basis for the terms "nitrous acid" and "sodium borohydride" in claim 44, as these terms are not present in claim 2.

Claim 44 has been amended to add reference to "wherein at least one of said reagents is an enzyme" Thus, as discussed above for claims 7 and 9, the transitional phrase "comprising," in claim 1 does not exclude treating the polysaccharides with additional elements such as chemical reagents. Therefore, Applicants assert that claim 44 as amended is in proper format and respectfully request that the rejection be withdrawn.

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Claim 42 stands rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner asserts that there is no support in the specification for a method of 2-O-sulfating Polysaccharide 10.

Claim 42 has been amended to recite a method of 2-O-sulfating Polysaccharide 11. As the Examiner concedes, Figure 20 supports a method of 2-O-sulfating Polysaccharide 11 (See Office action at page 12). Accordingly, Applicants believe that claim 42 is fully supported by the Specification and respectfully request that the rejection be withdrawn.

#### **Rejection Under 35 U.S.C. § 101**

Claims 11-13, 18, 20 and 22-31 stand rejected under 35 U.S.C. § 101. The Examiner asserts that the claimed methods have the same characteristics as found in nature and thus are not patentable subject matter.

Applicants have amended claims 11 and 12 to recite “wherein said treating is conducted *in vitro*.” Support for the amendment can be found, for example, at column 1 paragraph [0010]. Further support can be found, e.g. at column 5 paragraph [0061] to column 7 paragraph [0078]; column 8 paragraph [0087] column 9 paragraph [0093] and in the Examples.

Applicants assert that *in vitro* methods differ from *in vivo* methods as the precise *in vivo* environment can not be fully imitated. Therefore, *in vitro* methods of the present invention do not have the same characteristics as those found in nature.

Accordingly, Applicants respectfully request withdrawal of the rejection.

#### **Rejections Under 35 U.S.C. § 102**

(i) In the Office Action, the Examiner rejected claims 1, 2, 6-10 and 13-17 under 35 U.S.C. § 102(b), as allegedly being anticipated by Wei *et al.* (PTO-892, page 1, Ref. U), Applicants respectfully disagree.

Applicants assert that Wei *et al.* do not teach “a method of preparing a sulfated polysaccharide capable of binding to a binding partner.” (emphasis added). Wei *et al.* only teach one step in the sulfation of a polysaccharide, the N-deacetylation-N-sulfation of the N-position of the glycosidic residue. The resulting incompletely sulfated polysaccharide is

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unable to bind to proteins known in the art. Wei recites “[h]eparan sulfate is a highly sulfated carbohydrate polymer that binds to....numerous proteins. The formation of these protein-binding domains in heparan sulfate is dependent on a series of biosynthetic reactions that modify the polysaccharide backbone; the initiating and rate limiting steps of this process are the N-deacetylation and N-sulfation of N-acetylglucosamine residues in the polymer.” (abstract, emphasis added). Therefore, Wei *et al.* cannot and does not anticipate present claims 1, 2 6-10 and 13-17. Accordingly, Applicants request withdrawal of the rejection.

(ii) In the Office Action, the Examiner rejected claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47 under 35 U.S.C. § 102(b), as allegedly being anticipated by Perrimon *et al.* (PTO-892, page 1, Ref. W). Applicants respectfully disagree.

Applicants assert that Perrimon *et al.* discusses the natural *in-vivo* process of sulfating an HSPG. Perrimon *et al.* discloses that “[p]recursor HS chains are initially synthesized in the Golgi as non-sulphated copolymers attached to HSPG core proteins.” (page 725 last paragraph on left column and first paragraph on right column, emphasis added). The HSPG’s are further modified *in vivo* by natural sulphation enzymes (*See* Figure 1, captions) The Examiner acknowledges that the saccharides described by Perrimon *et al.* are modified by the Golgi enzymes (*See* page 14 of the Office Action).

Applicants have amended claims 1 and 2 to add reference to “*in vitro*.” As discussed above, *in vitro* processes differ from *in vivo* processes due to the different chemical environment and different conditions employed. Therefore, Perrimon’s disclosure of the natural HS sulphation processes does not anticipate Applicants claimed invention. Accordingly, Applicants request withdrawal of the rejection.

(iii) In the Office Action, the Examiner rejected claim 39 under 35 U.S.C. § 102(b), as allegedly being anticipated by Kusche *et al.* (PTO-892, page 2, Ref. U). The Examiner alleges that Kusch discloses the claimed method of synthesis of Polysaccharide 2 (*See* Page 16 of the Office Action). Claim 39 has been amended to delete reference to a method of synthesis of polysaccharide 2, thereby rendering the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

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### **Rejections Under 35 U.S.C. § 103**

- (i) In the Office Action, the Examiner rejected claim 42 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Perrimon *et al.* (PTO-892, page 1, Ref. W), in view of Kobayashi *et al.* (PTO-892, Ref. X, abstract). Applicants respectfully disagree.

Applicants assert that as discussed above, Perrimon describes the natural process of sulfation as occurs *in vivo*. Such *in vivo* process is different from the *in vitro* process which is the subject matter of the present claims. Kobayashi does not cure the deficiencies of Perrimon.

Accordingly, Perrimon and Kobayashi, when taken alone or in combination, do not teach, suggest or disclose the presently claimed invention. Applicants respectfully request withdrawal of the rejection.

- (ii) In the Office Action, the Examiner rejected claims 43 and 45 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Perrimon *et al.* (PTO-892, page 1, Ref. W), as applied to claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47, in view of Kusche *et al.* (PTO-892, page 2, Ref. U), Nader *et al.*, (PTO-892, page 2, Ref. V), Myette *et al.* (PTO-892, page 2, Ref. W) and Bick *et al.* (PTO-892, page 2, Ref. X). Applicants respectfully disagree.

As discussed above, Perrimon describe the natural process of sulfation as occurs *in vivo*. Such *in vivo* process is different from the *in vitro* process which is the subject matter of the present claims. The secondary references cited by the Examiner do not cure the deficiencies of Perrimon. Accordingly, Perrimon and the secondary references, when taken alone or in combination, do not teach, suggest or disclose the presently claimed invention. Applicants respectfully request withdrawal of the rejection.

- (iii) In the Office Action, the Examiner rejected claim 48 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Perrimon *et al.* (PTO-892, page 1, Ref. W), as applied to claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47, in view of Kovensky *et al.* (PTO-892, page 3, Ref. U). Applicants respectfully disagree.

As discussed above, Perrimon describe the natural process of sulfation as occurs *in vivo*. Such *in vivo* process is different from the *in vitro* process which is the subject matter of the present claims. Kovensky does not cure the deficiencies of Perrimon. Accordingly,

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Perrimon and Kovensky, when taken alone or in combination, do not teach, suggest or disclose the presently claimed invention. Applicants respectfully request withdrawal of the rejection.

(iv) In the Office Action, the Examiner rejected claim 63 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kusche *et al.* (PTO-892, page 2, Ref. U). The Examiner alleges that Kusch *et al.* teach the ability of solubilized mastocytomas microsomes to sulfate a series of pentasaccharides in the presence of [<sup>35</sup>S]PAPS (See page 22 of the Office Action). The Examiner further alleges that it would have been obvious for one of ordinary skill in the art to modify the non-sulfated pentasaccharide to produce a sulfated compound that is capable of binding to the antithrombin-binding region (See page 24 of the Office Action). Applicants respectfully disagree.

Claim 63 is directed to a method for producing pentasaccharide 15, comprising treating pentasaccharide 14 with a 3-O-sulfating reagent. The Examiner concedes that Kusch *et al.* do not teach a method of producing pentasaccharide 15 as instantly claimed, by 3-O sulfating pentasaccharide 14. Applicants assert that the method for producing pentasaccharide 15 of the present invention does not involve the modification of a non-sulfated pentasaccharide as described by Kusch (see synthesis steps in Figure 20). The synthetic approach of the present invention is different from the synthetic route described by Kusch. One of ordinary skill, upon reading Kusch, would not have been motivated to prepare pentasaccharide by -O sulfating pentasaccharide 14, and would have had no expectation that such route would be successful. Accordingly, Kusch *et al.* do not render obvious claim 63. Applicants respectfully request withdrawal of the rejection.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

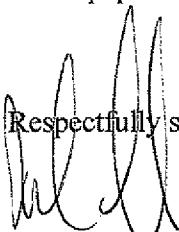
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